REMARKS

A. Status of the Claims and Amendments

Claims 1-32 were filed in the instant application. Claims 2-11 and 14-24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1, 12, 25, 27, 28, 29, and 31-32 stand rejected under 35 U.S.C. §102(b) as being anticipated by Herrmann *et al.* Claims 1-2, 12, 25, 27, 28, 29, and 31-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Herrmann *et al.* Claims 1-2, 11-25, 27-29 and 31-21 stand rejected under U.S.C. §103(a) as being unpatentable over WO 99/00120. Claims 1, 3-10, 12, 25-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Herrmann et al. in view of either Sugarman., Ranade, Mayer *et al.*, or Weiner *et al.* Claims 1 and 3-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/00120 in view of either Sugarman, Ranade, Mayer *et al.*, or Weiner *et al.* The specific grounds for rejection and applicants' response to them are set forth in detail below.

Claims 1-2, 4, 11, 14-24, 26, and 30-32 have been amended at the suggestion of the examiner to expedite the prosecution of this application. Claim 3 is canceled herein for containing subject matter that is already encompassed by the existing claims. Support for the amended claims is found within the specification. These amendments do not introduce new matter. Therefore, claims 1-2 and 4-32 are presented for reconsideration.

B. Rejection Under 35 U.S.C. § 112

Claims 2-11 and 14-24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the examiner, claim 3 should read "at least one of the lipids is a phospholipid." Claim 3 is canceled and claim 1 has been amended to better

state the invention. Applicants believe that these amendments should satisfy the examiner's concerns on this issue.

Additionally, the examiner states that the expression, "imexon or derivative thereof is hydrophobic" in claim 11, is confusing because imexon itself is water soluble. The examiner is correct in stating that imexon is water-soluble. However, several imexon derivatives have been found to by hydrophobic as supported by page 4, line 14 and page 8, line 10 of the specification. Therefore, claim 11 has been amended to read "wherein the imexon derivative is hydrophobic" to better state the invention.

The examiner also suggests that the chemical names be recited for the compounds in claims 14-24. Applicants have amended claims 14-24 to include the chemical names of the compounds as per the examiner's suggestion.

In view of these amendments, Applicants respectfully request that the rejection of claims 2-11 and 14-24 under 35 U.S.C. §112, second paragraph be withdrawn.

C. <u>Rejection under 35 U.S.C. § 102(b)</u>

Claims 1, 12, 225, 27, 28, 29, and 31-32 stand rejected under 35 U.S.C. §102(b) as being anticipated by Herrmann *et al.* (Herrmann). The examiner contends that Herrmann discloses compositions containing imexon and a lipid, specifically magnesium stearate. Applicants traverse.

Applicants have amended the claims to recite a pharmaceutical composition comprising imexon and its derivatives in combination with one or more ***phospholipids***. This amendment clearly distinguishes the current claims from Herrmann. Herrmann only discloses compositions of imexon with one species of lipid, magnesium stearate. Magnesium stearate belongs to a class of lipids known as the fats and oils. In contrast, phospholipids are an entirely different class of

lipids that contain phosphate groups. Anticipation requires that each and every element of the claimed invention be described, either expressly or inherently, in a single prior art reference. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1327, 58 U.S.P.Q.2d 1545, 1552 (Fed. Cir. 2001); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Because Herrmann does not disclose the use of imexon with one or more ***phospholipids***, Herrmann does not teach each and every element of the claims as amended.

Accordingly, it is believed that the claims as amended are not anticipated by Herrmann. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

D. <u>Rejection under 35 U.S.C. § 103(a) over Herrmann *et al.*</u>

Claims 1, 3-10, 12, and 25-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Herrmann. This reference teaches imexon compositions containing the lipid, magnesium stearate, as well as suggesting the use of an oil (such as olive oil) for the administration of imexon. The examiner argues that it would have been obvious to one of ordinary skill in the art to use an oil as a carrier to administer hydrophobic derivatives of imexon or suspension forms or oil micelles based on the suggestion of Herrmann. Applicants traverse.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and

not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if even one element is missing, a *prima facie* case of obviousness does not exist.

The first step in establishing a *prima facie* case of obviousness is presenting evidence that Herrmann teaches or suggests all of the claim limitations of Applicants' present claims. Applicants have amended claim 1 to recite "a pharmaceutical composition comprising an imexon or derivative thereof in combination with one or more ***phospholipids***." Claim 2 has been amended to read "wherein at least a portion of the ***phospholipids*** comprise micelles." Herrmann only discloses an imexon composition containing magnesium stearate. Additionally, Herrmann discloses only the use of an oil for the administration of imexon in micelles. Oil and magnesium stearate belong to the species of lipids known as fixed oils. On the other hand, phospholipids are a completely different species of lipids containing phosphorus. Because Herrmann does not teach an imexon composition containing a phospholipid, it does not teach or suggest all of the claim limitations found in claim 1. Thus, Herrmann fails to establish a necessary element required for a *prima facie* case of obviousness.

Another element that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify Herrmann. Clearly, there is no suggestion or motivation in Herrmann for the use of phospholipids in the administration of imexon as amended in the claims. Herrmann discloses compositions in conjunction with only fixed oils, a single species of lipids, with imexon. No mention is ever made in Herrmann regarding phospholipids, or even lipids in general. Moreover, phospholipids have different properties compared to fixed oils. When mixed with water, phospholipids tend to form bilayers rather than micelles. Moreover, Herrmann teaches use of magnesium stearate in

administration of imexon in film tablet form. A skilled artisan would know that phospholipids would not be used in tablet form, but rather in intravenous administration. One skilled in the art would not be motivated to make compositions of imexon and phospholipids or use phospholipids in the administration of imexon based on the teachings of Hermann. As such, Herrmann fails to establish another element required for a *prima facie* case of obviousness.

A third element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of Herrmann would be successful. The examiner has produced no evidence that one skilled in the art would interpret the teachings in Herrmann to encompass success in use of phospholipids. Significantly, Herrmann never expressly states that use of imexon with phospholipids would reasonably be expected to be successful. On the contrary, Herrmann teaches that use of oils with imexon ***may*** be successful. As stated previously, oils and phospholipids have different properties. A skilled artisan would know that a reasonable expectation of success in using oils would not automatically correlate to a reasonable expectation of success in using phospholipids. At most, Herrmann merely presents an "obvious to try" situation. The Federal Circuit has repeatedly held that an "obvious to try" suggestion will ***not*** render the claim obvious. *In re Roemer*, 258 F.3d 1303, 59 U.S.P.Q.2d 1537 (Fed. Cir. 2001). Thus, a person of ordinary skill in the art would not reasonably expect the use of phosholipids to be successful by modifying Herrmann.

Because the examiner has failed to present a *prima facie* case of obviousness on all three elements, the Applicants respectfully request that the rejection of claims 1, 3-10, 12, and 25-32 be withdrawn.

E. Rejection under 35 U.S.C. § 103(a) over WO 99/00120

Claims 1-2, 11-25, 27-29 and 31-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/00120 (WO '120). This reference is cited as disclosing the use of vegetable oil for the preparation for the slurry of the imexon compounds for administration. The examiner argues that it would have been obvious to one of ordinary skill in the art to use an oil as a carrier to administer imexon or hydrophobic derivatives of imexon or suspension forms or oil micelles based on the suggestion of WO '120. Applicants traverse.

The first step in establishing a *prima facie* case of obviousness is presenting evidence that WO '120 teaches or suggests all of the claim limitations of Applicants' present claims. As stated before, Applicants have amended claim 1 to recite "a pharmaceutical composition comprising an imexon or derivative thereof in combination with one or more ***phospholipids***." Additionally, as mentioned previously, Applicants have amended claim 2 to encompass only ***phospholipids***. WO '120 only teaches the use of vegetable oil for the administration of imexon and its derivatives. Again, vegetable oil and phospholipids are two different species of lipids. Because WO '120 does not teach an imexon composition containing a phospholipid, it does not teach or suggest all of the claim limitations found in claim 1. Thus, WO '120 fails to establish a necessary element required for a *prima facie* case of obviousness.

The second element that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify WO '120. No suggestion or motivation exists in WO '120 for the use of phospholipids in the administration of imexon or its derivatives as amended in the present claims. WO '120 only teaches use of vegetable oils in the administration of imexon and its derivatives. Phospholipids or lipids are not mentioned once in WO '120. As discussed before, one skilled in the art would know that

phospholipids and oils have very different aggregation properties. Furthermore, WO '120 describes the use of oils in preparing soft ***gelatin capsules***. One skilled in the art knows that phospholipids are more suitable for ***intravenous*** delivery of drugs than for capsule formulations. Thus, no motivation exists to use phospholipids in the administration of imexon or its derivatives based on the teachings of WO '120. As such, WO '120 fails to establish an element required for a *prima facie* case of obviousness.

The final element necessary to establish a *prima facie* case of obviousness is that the reference must show a reasonable expectation of success. Again, the examiner fails to present any evidence in WO '120 showing the use of phospholipids with imexon and its derivatives would be reasonably expected to succeed. The passages that the examiner cites in WO '120 do not support such a conclusion whatsoever. WO '120 discloses that the use of "an acceptable vegetable ***oil***, light liquid petrolatum or other inert ***oil***" may result in success (emphasis added). Nothing in WO '120 suggests that use of phospholipids or even non-oil lipids with imexon and its derivatives would be successful. Since one skilled in the art would know that phospholipids and oils possess different properties, success could not be reasonably expected.

Additionally, WO '120 is cited as suggesting that use of oils in administration of imexon and its derivatives via soft gelatin capsules would be successful. One of skill in the art would know that use of phospholipids in the administration of drugs is typically performed intravenously. From the examiner's single citation, a skilled artisan would not reasonably expect that intravenous administration of imexon and its derivatives using phospholipids be successful. The examiner appears to be erroneously using hindsight in view of the invention itself to support his obviousness rejection. A single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness. *Bausch and Lomb, Inc. v. Barnes Hund/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q.2d 416 (Fed. Cir. 1996).

Furthermore, this is an "obvious to try" situation which, as mentioned before, is the incorrect standard for obviousness. As a result, the examiner has not succeeded in establishing the final element of a *prima facie* case of obviousness.

Therefore, because the examiner has failed to present a *prima facie* case of obviousness on all three elements, the Applicants respectfully request that the rejection of claims 1, 3-10, 12, and 25-32 be withdrawn.

F. Rejection under 35 U.S.C. § 103(a) over Herrmann *et al.* in view of Sugarman, Ranade, Mayer *et al.*, or Weiner *et al.*

Claims 1, 3-10, 12, 25-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hermann, further in view of either of the following references: Sugarman, Ranade, Mayer *et al.* (Mayer), or Weiner *et al* (Weiner). The examiner argues that the use of liposomes as carriers for imexon would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer, and Weiner. Applicants traverse.

As mentioned above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. If any one element is missing, a *prima facie* case of obviousness does not exist.

One of the elements that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Herrmann in view of either Sugarman, Ranade, Mayer, and Weiner. "The mere fact

that references can be combined or modified does not render the resultant combination obvious ***unless the prior art also suggests the desirability of the combination***." *Manuel of Patent Examining Procedure* (MPEP) § 2143.01 (8th Ed. Rev.) (emphasis added). None of these references makes any suggestion of delivering imexon via administration of liposomes. Herrmann discloses delivery of imexon with ***oils***, not phospholipids or liposomes. Similarly, Sugarman, Ranade, Mayer, and Weiner teach the use of liposomes in drug delivery, but never mention imexon as a possible drug.

Consequently, the issue is whether one of ordinarily skill in the art, with knowledge that is generally available, would be motivated to combine Herrmann in view of either Sugarman, Ranade, Mayer, and Weiner. Applicants disagree that one of ordinary skill in the art would be motivated to combine these references. Many drug therapies have been investigated in treating cancer, but in two of the references that discuss liposomal drug delivery, Mayer and Weiner, only one drug is mentioned, doxirubicin. None of these references make any recommendations as to which cancer drugs may be suitable for liposomal delivery other than doxirubicin. Sugarman states that "most of the chemotherapeutic agents used have been doxorubicin or cisplatin derivatives." Sugarman also mentions use of muramyl peptides with liposomes. Ranade discloses use of liposomes with doxirubicin, cisplatin, and macrophage activation factors. However, none of the drugs mentioned have any similarity or structural resemblance to imexon. Hundreds of drugs exist for treating cancer such that one skilled in the art could not possibly know that imexon would be a drug appropriate for liposomal delivery. Furthermore, since Herrmann does not explicitly state that such use would be possible, one skilled in the art would have even less motivation to combine the references. Therefore, Herrmann in view of either Sugarman, Ranade, Mayer, and Weiner fails to establish an element necessary for a *prima facie* case of obviousness.

Another element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of Herrmann in view of either Sugarman, Ranade, Mayer, and Weiner would be successful. Applicants submit that there would be no reasonable expectation of success in combining imexon and liposomal delivery in treating cancer. The examiner presents no evidence that combining imexon and liposomes would reasonably result in success. The result of combining drug therapies is impossible to predict. The examiner appears to assume that combining imexon and liposomal drug delivery will automatically result in success. There simply is no basis for such an assumption. Furthermore, none of the five references provide any guidance or recommendations as to whether combining imexon with liposomal drug delivery would be successful in treating cancer. At best, the prior art presents an "obvious to try" situation. Specifically, the combination of imexon and liposomal delivery may or may not be successful. However, the PTO's reviewing court has consistently held that "'obvious to try' is not the standard" and "does not render a claim obvious." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 U.S.P.Q.2d 1065 (Fed. Cir. 2000), *In re Roemer*, 258 F.3d 1303, 59 U.S.P.Q.2d 1537 (Fed. Cir. 2001). In view of the prior art, a person of ordinary skill in the art could not reasonably expect to achieve success in administering imexon via liposomal delivery. As a result, WO '120 in view of either Sugarman, Ranade, Mayer, and Weiner does not establish a reasonable expectation of success as required for a *prima facie* case of obviousness.

The examiner has not established a *prima facie* case that claims 1, 3-10, 12, 25-32 were obvious at the time of filing. Accordingly, applicants respectfully request that the rejection of claims 1, 3-10, 12, 25-32 be withdrawn.

G. **Rejection under 35 U.S.C. § 103(a) over WO 99/00120 in view of Sugarman, Ranade, Mayer *et al.*, or Weiner *et al.***

Claims 1, 3-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO '120, further in view of either of the following references: Sugarman, Ranade, Mayer, or Weiner. The examiner argues that the use of liposomes as carriers for imexon and its derivatives taught by WO '120 would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer, and Weiner. Applicants traverse.

In light of the reasons presented in Section F, above, Applicants disagree that claim 1, 3-32 are obvious over WO '120 in view of either Sugarman, Ranade, Mayer, or Weiner. Furthermore, Applicants submit the following arguments against the examiner's assertion of obviousness.

An element that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of WO '120 in view of either Sugarman, Ranade, Mayer, or Weiner. None of these references make any suggestion of using liposomes as a carrier of imexon and its derivative.

Therefore, the relevant inquiry is whether one of ordinarily skill in the art, with knowledge that is generally available, be motivated to combine WO '120 in view of either Sugarman, Ranade, Mayer, and Weiner. Applicants disagree that one of ordinary skill in the art would be motivated to combine these references. Applicants reiterate that many therapies and drugs are available in treating cancer. Although Sugarman provides examples of using liposomes as a carrier of cancer drugs such as doxirubicin and cisplatin, it does not suggest which additional cancer drugs could be delivered using liposomes. As a matter of fact, neither Ranade, Mayer, or Wiener makes any recommendation as to potential types of cancer drugs which may warrant future investigation. In view of the myriad of cancer drugs available and the lack of

suggestion in the prior art, a skilled artisan would have no motivation to specifically use liposomes as a carrier for imexon and its derivatives. Thus, WO '120 in view of either Sugarman, Ranade, Mayer, and Weiner fails to establish an element required for a *prima facie* case of obviousness.

Another element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of WO '120 in view of either Sugarman, Ranade, Mayer, and Weiner would be successful. Applicants submit that there would be no reasonable expectation of success in combining imexon derivatives and liposomal delivery in treating cancer. The examiner presents no evidence that combining imexon derivatives and liposomes would reasonably result in success. In fact, Sugarman states that "liposomal delivery of antitumor therapy is in its ***infancy*** and the optimal liposome/drug formulation has ***not yet been determined.***" Clearly, in view of this statement, one of ordinary skill in the art would understand that using liposomes as carriers of imexon and its derivatives would not reasonably result in success.

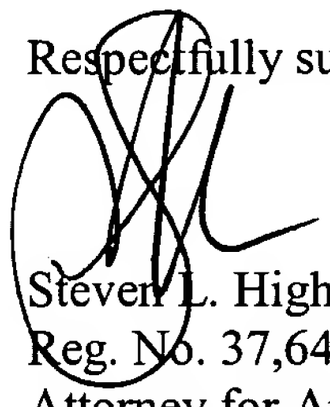
Furthermore, combining cancer drug therapies is a highly unpredictable art. Trial and error is often required to determine the proper combination of therapies. For example, Sugarman discloses use of liposomes as a carrier for doxirubicin delivered intravenously. In one of the studies, out of 18 patients available for study, only 5 exhibited a ***marginal*** response. Sugarman, page 233. These results strongly suggest that success is not even reasonably expected for well-known cancer drugs. As mentioned in section F, the prior art, at most, describes an "obvious to try" situation which does not render a claim obvious. Accordingly, the examiner has not established an element necessary for a *prima facie* case of obviousness.

In view of the examiner's failure to satisfy all three elements needed for a *prima facie* case of obviousness, the Applicants respectfully request that the rejection to claims 1 and 3-32 be withdrawn.

H. Conclusion

Applicants have submitted arguments that are believed to overcome all outstanding rejections. Therefore, allowance of this application is solicited. In the event that the Examiner has suggestions regarding claim amendments or additional information that might speed this case toward allowance, the Examiner is requested to contact the Applicants' representative listed below.

Respectfully submitted,



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